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# Workshop 6.5

# Endocrine active substances and the need to improve environmental protection: An environmentalist's perspective*

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*Abstract*: This paper reviews the existing concerns and presents conclusions and recommendations for action.

The first section outlines an environmentalist's perspective and predicts that endocrine active substances (EASs) pose a high risk for wildlife populations. The second section explains that risk assessment, as currently practiced for individual chemicals, does not adequately protect the environment, and suggests several improvements that should be made. However, it is argued that the properties of endocrine disruption lead to increased uncertainty in the risk assessment, such that countries wishing to achieve a high level of protection would be justified in implementing precautionary controls.

The third section outlines some conclusions and additionally provides an appraisal of the responses of governments and industry. Furthermore, several recommendations are made, particularly the imperative for research funding to be substantially increased and guaranteed for many years to come. Also highlighted is the need to hasten the development of screens and tests for ecotoxicity, and for governments to commit to a comprehensive sorting, screening, and toxicity testing program for all chemicals to which significant exposure occurs.

## AN ENVIRONMENTALIST'S PERSPECTIVE OF RISKS OF ENDOCRINE ACTIVE SUBSTANCES (EASs) TO WILDLIFE

The term "risk assessment" is typically used to describe "the *estimation* of the incidence and severity of the adverse effects likely to occur in an environmental compartment due to actual or predicted exposure to *a substance*" [1]. Thus, to many scientists working on chemicals, the term "risk assessment" suggests a detailed assessment of the studies that have been undertaken on an individual chemical. This is a very narrow "reductionist" focus, which merely seeks to determine whether a chemical is individually found in the environment at levels in excess of its predicted no-effect concentration (PNEC).

In attempting to establish the potential scope of the threat that EASs pose to wildlife, it is important to evaluate the bigger picture. Despite the lack of understanding regarding the full consequences of the phenomenon of endocrine disruption (ED), this section argues that in order to identify appropriate policy responses to EASs, likely environmental risks must be assessed both at the micro or single-substance level, and at the macro level. The term "macro-level risk assessment for endocrine disruptors" is

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coined to refer to an estimation of whether adverse effects are likely to occur, and the possible severity of those effects, due to current exposures to EASs in general, some of which may not yet be identified.*

As noted above, the evaluation of risk is not an exact science, but rather it is "an estimation". Thus, risk assessment should evaluate and use available scientific data, but it should also be able to consider expert judgement or "best guesses" where scientific data are not available.

At the macro level, several questions are pertinent, including the following:

a) Is the environment exposed to EASs?
b) Could critical effects in wildlife populations be passing unnoticed?
c) Are suspected EASs adequately controlled, and are more EASs likely to be identified in the future?
d) Are many species likely to be under threat?

Finally, in light of the responses to the above questions, is it likely that endocrine EASs, either singly or in combination, are causing effects in wildlife that might impact at the population level?** These questions are answered below.

a) Chemical monitoring data confirm that EASs are found in the environment [3,4], and studies show that local wildlife populations have already been adversely affected. In many countries, sublethal effects due to EASs have been reported in fish [see 5,6].

   However, although certain chemicals with endocrine active properties have been found in the environment, there is insufficient environmental monitoring to determine the range of chemicals that are actually present. Global chemical production has escalated in recent decades from around 1 million tonnes per year in 1930 to around 400 million tonnes by the year 2000 [7]. This will no doubt have led to a dramatic increase in the exposure of the environment to a myriad of chemicals, including EASs.

b) Critical effects in wildlife populations could certainly be passing unnoticed for many reasons, not least the paucity of environmental monitoring. Trends in many endocrine endpoints, such as the occurrence of intersex, or even population trends, cannot be easily ascertained for most species. The diversity of ways in which chemicals can influence endocrine systems also makes it difficult to identify such effects in the wild. Even in different fish species exposed to the same estrogenic compounds, it appears that the effects may vary. Thus, several fish species show intersex characteristics and vitellogenin production on exposure to estrogens, while male sand gobies exhibit feminization of the urogenital papilla [8].

   Numerous wildlife populations have declined without the precise causes for these declines being known in many cases. The living planet index, which integrates data on the abundance of 282 forest species, 195 freshwater species, and 217 marine species, shows an overall decline of about 37 % between 1970 and 2000 [9]. Globally, species are being lost at an alarming rate, and many are insecure. In the United States, for example, it is suggested that one-third of the native flora and fauna is at risk [10]. This lends weight to the need for a more cautious approach to pollution control. Habitat destruction is often implicated in the decline of wildlife, but this paper conjectures that pollutants such as EASs *might* be partly responsible in some cases.

   Neurological alterations, leading to behavioral effects, often represent the earliest observable manifestation of toxicity. However, effects on behavior may be subtle and difficult to recog-

*Theo Colborn could be said to have pioneered the technique of macro-level risk assessment, in that in 1991 she brought together experts to agree to the now famous Wingspread consensus statement on EASs [2]. By getting consensus amongst recognized experts, she gave legitimacy to the technique, which by its nature is even more subjective than micro risk assessment.

**Unlike human health risk assessors, ecotoxicologists in the EU risk assessment process do not strive to protect every single fish, but rather the fish *population*. Thus, the ultimate aim of the risk assessment for the environment is to protect the structure and function of ecosystems, and so the protection goal is at the population or community level [11,12].

nize, and some species are particularly difficult to study. It is speculated that effects on behavior might be responsible for some wildlife species being less able to escape predation, rear offspring, or cope with the stress of a changing environment. Such speculation is not unreasonable, as the developing nervous system is especially vulnerable to toxicants. Furthermore, in humans, in utero exposure to PCBs (polychlorinated biphenyls), which have been shown to disrupt thyroid hormones in laboratory experiments [13], has been linked to intellectual impairment in children [14–16]. Indeed, chemicals with endocrine active properties have already been associated with behavioral effects in some wildlife species. Lack of parental attentiveness, for example, has contributed to reproductive problems in Forster's tern [17]. However, although behavioral effects attributed to pollutants have been reported in birds nesting in colonies [18], it is more difficult to pick up effects in birds that nest individually. Nevertheless, recent studies suggest that pollutants may be affecting behavior and egg hatchability in male kestrel (*Falco sparverius*) [19]. Other effects on reproduction and sex-specific behaviors may be missed in the wild. In the laboratory, for example, estrogen exposure has been shown to affect songbirds, causing females to sing like males [20].

Critical effects in wildlife populations may also be passing unnoticed because delays can occur between exposure and the effects becoming evident. For example, adverse effects on an animal's ability to reproduce may not be evident until the animal reaches maturity. Transient or even "one-off" exposure to certain pollutants during developmental periods can result in irreversible effects in later life [21]. Effects may also be delayed because it may take some time before pollutants build up in biota to reach levels able to cause harm. EASs are certainly being passed on in the food chain. For example, experiments with male flounder showed that they did not produce vitellogenin (the female egg yolk protein) when caged in estrogen-contaminated estuaries in the United Kingdom. However, when fed on mussels (*Mytilus edulis*) that had been kept in the industrially contaminated Tees, they did show vitellogenin induction [22]. Attention should not just be focused on lipophilic compounds, because other chemicals may be building up to harmful levels in certain organs, or in blood. For example, PFOS (perfluorooctane sulfonate), a chemical with thyroid-disrupting properties, has been found bound in the blood of numerous wildlife species throughout the world [23].

Moreover, the full effects of even well-studied EASs may take years to come to light, even in species for which data would be expected to be well scrutinized. For example, DDT was shown to affect reproduction in birds back in the 1960s, but it was not until 2001 that new research was published linking this pollutant to low infant birth weight and premature births in the United States [24]. The effects of EASs may also pass unrecognized because effects and even deaths may be solely attributed to natural causes like disease. For example, researchers have suggested that impaired immune function due to pollutants may have been at least partly to blame for the mass mortality in some cetacean populations [25–27]. The endocrine system plays an important role in the function and development of the immune system, and so disruption might result in increased susceptibility to disease.

c) Chemicals that are already suspected to be EASs are not adequately controlled. This is because in the past, toxicity tests did not evaluate endocrine endpoints adequately, and potential low-dose effects were not fully investigated. Also, many toxicity assessments were not conducted on sensitive life stages (e.g., early life stages and during times of rapid cell replication). Thus, the potency of many substances may be significantly underestimated. Furthermore, for many chemicals, even basic toxicity data are lacking, such that it is a fair assumption that more EASs will be identified in future.

d) Many species are likely to be under threat, as the way in which the endocrine system works shows many similarities between species. For example, some steroid hormones found in mammals are also found in other vertebrates, such as fish and amphibia, as well as in some invertebrate groups, such as mollusks. Unfortunately, relatively few species have been examined for their responses to

man-made hormone-disrupting chemicals, and therefore it is not possible to predict the most sensitive species, nor is it possible to predict the most critical endpoints in most species. Effects may not even be limited to animals, as estrogen-mimicking chemicals may affect plant growth by disrupting the process of nitrogen fixation [28].

### Macro risk assessment conclusions

The endocrine system includes a wide range of organs and hormones, such that there is a vast number of potential ways in which the system can be disrupted. Man-made EASs are certainly found in the environment, and it is likely that critical effects in wildlife populations are passing unnoticed. Also, given the lack of toxicity data on the bulk of chemicals in commerce today, many currently unsuspected chemicals may in the future be found to contribute to endocrine-disrupting effects. EASs may act together in an additive or more than additive manner. Even currently suspected chemicals may not be adequately controlled, because low-dose effects have not yet been properly investigated, and current toxicity testing regimes may not pick up endocrine disruption. Many species could potentially be under threat, because the endocrine system has many similarities in living creatures from different phyla. Finally, given all these concerns, it can be concluded that there is a very real likelihood that EASs will, in the future, be found to be causing population-level effects in many more wildlife species. Thus, the macro-level risk assessment predicts that EASs pose a high risk for wildlife populations. It is certainly reasonable to suggest that the scale of the phenomenon of endocrine disruption is likely to be considerably greater than currently known, and that many wildlife populations may be impacted.

## AN ENVIRONMENTALIST'S PERSPECTIVE ON IMPROVEMENTS THAT NEED TO BE IMPLEMENTED IN FRAMEWORKS TO ASSESS THE RISKS OF INDIVIDUAL CHEMICALS

This section focuses on risk assessment, as it is the central pillar of chemical-based legislation, which provides controls over the registration, marketing, and use of substances. However, it must be recognized that controls over the marketing and use of certain chemicals do not preclude the need for extensive environmental monitoring and surveillance. This must operate in tandem to identify and prevent effects both from substances that are not marketed (e.g., natural hormones found in sewage effluents, degradation products, and unwanted by-products), and from substances that have either not undergone hazard and risk assessment, or are being used in a harmful manner.

Formal frameworks for assessing the risks from individual chemicals are laid down in various national and regional legislative regimes, but unfortunately these tend to ignore important concerns. Such omissions undermine the validity of these assessments. For example, because it is difficult to find a scientifically acceptable way of dealing with the complexity, risk assessment tends to ignore the likelihood of possible additive effects. Also, the likely ramifications for wildlife populations of subtle effects from low-level exposures are often largely ignored, as it is difficult to show whether or not these effects will affect the population level. Scientists performing risk assessments seem loath to make predictions about these concerns, because few robust scientific data are available.

Several of the key improvements that need to be implemented in the risk assessment of individual chemicals are listed below:

- Substances should be tested at low doses. Hormone-disrupting chemicals modulate a system that is physiologically active. Therefore, the traditional assumption that there is a threshold dose that must be exceeded before a response is seen may not apply. Receptor-mediated responses can first increase and then decrease as the dose increases, due to receptor down-regulation and other compensatory responses. Thus, it should not be assumed that dose–response relationships are always

monotonic, because this is contradicted by many examples from the literature [29,30]. The potential low-dose effects on behavior should be fully evaluated.

- There is a need to try to minimize animal testing, but it may not be sufficient to look for effects in just one or two species, because it is widely accepted that there may be remarkable species variation in the sensitivity to chemicals. In particular, there is a need to develop test methods for amphibia and invertebrates, and sentinel species need to be identified. Mollusks, for example, seem particularly sensitive to certain EASs. In addition, if exposure is likely to occur, tests may need to be undertaken to determine the potential effects on birds and on plants. A battery of tests may therefore be necessary, particularly given the diverse physiological mechanisms in different animals. As an example, eggshell thinning in birds would not be predicted by testing on mammals, fish, or invertebrates.
- In the risk assessment of an individual chemical, the possibility for additive or interactive effects due to combinations of substances should be considered, where exposure need not be simultaneous or via the same route.* There is already evidence to suggest that the exposure to several EASs may result in a combined response more than the threshold for effects, even though individually each chemical is below its effect level [31,32]. Risk assessment as currently practiced usually only evaluates the effects of the individual chemical on a previously unexposed laboratory animal, but in the real world an animal may be exposed to a variety of substances, via several exposure routes, including air, water, and food, as well as from the remobilization of contaminants already stored in the organism's adipose tissue. It will be exceedingly difficult to accurately predict the interactive effects of exposure to numerous hormonally active substances at varying concentrations. Possible options for dealing with this might include the imposition of further "safety" or "assessment factors" in the risk assessment, or the development of a toxic equivalent factor approach. However, some researchers have already identified that a toxic equivalent factor approach, as used for dioxin and dioxin-like PCB mixtures, is unlikely to be a useful approach for these compounds, because EASs may behave in an additive manner for some effects, but antagonistic for others [35]. Risk assessment of chemicals should also always be based on aggregate risk, such that all exposure routes to the substance should be considered.**
- A more prudent approach (that is, a more cautious approach) should be brought to bear when deciding whether subtle low-dose effects are likely to affect human health or to impact the population level of wildlife. The burden of proof should be lowered such that regulations should deliver "reasonable certainty of no harm". This is explained in more detail below, where the European Union (EU) situation is used as an example.

## The need for a more prudent approach in risk assessment

Much of the recent heated debate on EASs has focused on conflicting studies relating to whether certain EASs, such as bisphenol A, can cause effects at very low-dose levels. In the future, science will hopefully resolve this issue. By 2002, low-dose effects due to bisphenol A had been reported in several species, including fish [36], mollusks [37], and mammals [38–43].

However, this debate may obscure more intractable reasons for differences in the perception of the risks from EASs. That is, what are the implications of some of the effects that can be attributed to

*As an example of such an omission, the potential additive effects due to concurrent exposure to di(2-ethylhexyl)phthalate (DEHP) and di(*n*-butyl)phthalate (DBP) are unable to be considered within the EU risk assessment of DEHP under the Existing Substances Regulation, despite the fact that exposure to several phthalates is likely [33], and that additivity has been shown to occur [34].

**The U.S. Food Quality Protection Act, for example, does consider the cumulative effects of pesticide residues and other substances that have common mechanisms of action, and also considers aggregate risk from non-food exposure.

low doses of EASs in laboratory experiments, and which effects should be taken forward in risk assessment to drive the regulation of these chemicals? As an Organization for Economic Cooperation and Development (OECD) document noted, "judgements are unclear and certainly not unanimous on issues such as whether or not hormonal effects without obvious toxic effects should be considered adverse" [44].

In the EU, the debate has been aired at the Technical Meetings for the Existing Substances Regulation. In these meetings, representatives from the Member States assess the risks of priority industrial chemicals, which were placed on the EU market prior to 1981. In the meetings discussing the risk assessment for humans, the implications of a positive result in the uterotrophic assay has been an area of disagreement. Representatives of the United Kingdom have argued that the dose of bisphenol A causing an increase in uterine weight in laboratory animals should not be taken forward in risk assessment. They consider that the uterotrophic assay is only a screening test, which while it can be used to indicate potential estrogenic activity, should not be used for risk characterization purposes because it does not measure functional changes in reproductive parameters. However, representatives from other Member States, such as Denmark and Sweden, disagree and have argued that an increase in uterine weight should be considered adverse.

The World Wildlife Fund (WWF) supports the Swedish and Danish viewpoint that effects on uterus weight should be taken forward in risk assessment. Exposure to xenoestrogens at levels causing biological effects should be considered undesirable. Indeed, an increased uterine weight is probably not the most sensitive endpoint for estrogenicity [45], such that even lower dose levels need to be taken forward in the risk assessment. Estrogenic effects should be considered undesirable because it is well known that increased exposure to endogenous estrogen increases the risk of breast cancer. Moreover, our knowledge of the roles played by hormones in unborn and newborn infants are still being unravelled, such that it would be better to be cautious about the possible long-term effects of perturbing normal function. It is, for example, interesting to note that during the first three months of life, male babies have high levels of male hormones (around 50 % of adult levels) [46,47]. It is not known exactly why this is, but it is believed that the subsequent behavior of the individual is imprinted at this time [48]. Therefore, interference in hormonal processes at this age could have significant consequences to development.

Similarly, in the EU Technical Meetings discussing the environmental risk assessment, there has been vigorous debate as to whether some of the effects that have been noted in laboratory experiments are liable to translate into an effect on fish population numbers. For example, in an experiment on fish exposed to bisphenol A, an effect on spermatogenesis was noted at a dose level lower than that causing effects on egg hatchability [36]. At the EU Technical Meeting in March 2001, the UK representative argued that only the dose level causing effects on egg hatchability should be used for risk assessment, since the lower dose causing effects on sperm could be disregarded, as it had been explicitly shown not to affect hatchability. However, other Member States were not satisfied, and did not want to dismiss the effects on spermatogenesis as unimportant for the risk assessment. This was because although effects on spermatogenesis may not affect the population level in the laboratory, this may not hold true in the wild, where a small difference in sperm count might well have an impact on reproductive performance.

Stuart Dobson of the UK Centre for Ecology and Hydrology has noted that the distinctions that are made between findings that are likely to affect the population level, and those that are not, may be unrealistic and somewhat artificial, since there is no accepted way of reliably determining which is which [49]. Even traditional endpoints, such as egg hatchability, have no definite population effect, since survival to adulthood and breeding is density-dependent. Thus, the distinction is deductive rather than scientific because there is no population dynamics component in the risk assessment process.

Opinions of EU technical experts have also been divided as to how to interpret other effects recorded in laboratory experiments. For example, low doses of bisphenol A have been shown to affect sword length in swordtail fish (*Xiphophorus helleri*) [50]. This is considered to be a secondary sexual characteristic in males, but UK experts did not consider that a reduction in sword length would impact

on the population level. The draft Risk Assessment Report, written by the UK rapporteur, stated, "The significance of the changes in sword length is not understood. It is thought that the length of the sword has an influence on mating success, with female fish preferring males with longer swords, but it is not clear what degree of change should be considered to be significant." However, it could be argued that altered pairing might make the population less able to cope with other stresses. The United Kingdom appears to want to be assured about the levels causing significant or population-level effects, but this approach is fundamentally flawed because it would be very difficult, if not impossible, to prove the ecological relevance of all the effects recorded in the laboratory. The UK approach is likely to reduce or potentially eliminate safety margins that *might* exist due to the imposition of assessment factors designed to take account of intra- and inter-species variations. Nevertheless, this is the situation that prevails.

WWF suggests that dose levels giving rise to effects that can be *reasonably predicted* to give rise to a population-level effect, should be taken forward in risk assessment. Thus, effects on spermatogenesis, sword length, or vitellogenin production should all be considered potentially adverse for the population, and these dose levels taken forward in risk assessment. The complexities of ecosystems, and the external threats they face, are such that the environment should be given the benefit of any doubt. If the population level of just one species is directly adversely affected, then this may have as yet unknown consequences for many other species. For example, tributyltin (TBT) caused imposex and decline in numbers of mollusks, but several other species were also affected [51–53]. Therefore, it is argued that there is a need for a more cautious or more prudent approach to be taken in risk assessment.

Similarly, in the United States there is a need to lower the hurdle that regulators have to climb before they can impose control measures. For example, the Toxic Substances Control Act (TSCA) requires that an "unreasonable risk" must be shown. However, environmentalists would argue that the burden of proof should be reversed and lowered, such that industry should have to provide data and regulations should deliver "reasonable certainty of no harm".

## JUSTIFICATION FOR INVOKING THE PRECAUTIONARY PRINCIPLE

Each member of the World Trade Organization has the independent right to determine the level of environmental or health protection that they consider appropriate. For countries that want to promote a high level of protection, making modifications to the risk assessment methodology may not be adequate. Instead, recourse to the precautionary principle may be justified for EASs.

Where the risk assessment indicates that there are reasonable grounds for concern that the desired level of protection for the environment (or future generations) could be jeopardized, then precautionary risk management can be taken, even though the scientific evidence is insufficient, inconclusive, or uncertain.

EASs have properties that specifically lead to increased uncertainty in the estimation of whether they pose an acceptable risk. Such increased uncertainty arises due to the greater potential for interactive effects, because EASs frequently act via a common mechanism of action, or via pathways that converge on a common mechanism of action. EASs also give rise to increased uncertainty in relation to potential low-dose effects (including behavioral effects), and what these might mean for the organism. Thus, EASs are likely to cause adverse effects in ways that challenge traditional risk assessment models. Given this, it is argued that precautionary action can be justified. In the EU, there have already been several notable political statements on the need to take precautionary action on EASs [54,55], although little concrete action to reduce the risks has yet been seen.

Opponents of the precautionary principle ridicule it as being a tool that can be used arbitrarily even in the absence of evidence that a hazard exists. This is not the case. The intent is that precaution can be invoked when the risk is unproven but nevertheless plausible in the light of existing scientific knowledge. The European Commission's communication on the precautionary principle states that recourse to the precautionary principle presupposes (a) the identification of potentially negative effects

resulting from a phenomenon, product, or procedure, and (b) a scientific evaluation of the risk, which because of the insufficiency of the data, or their inconclusive or imprecise nature, makes it impossible to determine with sufficient certainty the risk in question [56].

Recourse to the precautionary principle might result in any one or more of a range of options, from requiring more research to implementing a ban on the chemical. Therefore, for example, a possible precautionary risk management option would be the imposition of a requirement to get permission before the EAS could be used, and to permit its use only in certain applications, considering its socio-economic benefits, the lack of safer chemicals, and measures to minimize exposure. Indeed, this is the approach that the EU may take to control the risks posed by these chemicals, an approach that is actively supported by WWF. Thus, in 2001, the Environment Ministers of the EU suggested that when scientifically valid test methods and criteria are available for EASs, then new EU legislation should require EASs to be subject to a prior authorization procedure [57]. However, as of 2003, the outcome of the EU review of chemicals legislation was still a matter of debate.

## CONCLUSIONS AND RECOMMENDATIONS

### Conclusions and appraisal of some government and industry responses

- To identify appropriate policy responses to EASs, there is a need to assess the likely environmental risks both at the *micro (*or single-substance level), and at the *macro level.* The term "macro level risk assessment for endocrine disruptors" is coined to refer to an estimation of whether adverse effects are likely to occur, and the possible severity of those effects, due to current exposures to EASs.
- The macro-level risk assessment predicts that EASs pose a high risk for wildlife populations. It is certainly reasonable to suggest that the phenomenon of endocrine disruption is considerably greater than currently known, because critical effects in wildlife populations are likely to be passing unnoticed.
- Risk assessment as currently practiced for individual chemicals does not adequately protect the environment, and improvements could be made.
- However, given the increased uncertainty in determining the risks posed by EASs, countries wishing to implement a high level of protection would be justified in taking precautionary action.
- Regulatory processes are clearly inadequate, in that many chemicals are currently marketed without even basic toxicity data being available [58–61]. Undoubtedly, industry has a legacy of neglect, and could do more to help develop new test methods, and to identify EASs using the available test methods.
- The U.S. government's response to the issue of endocrine disruption has been praiseworthy, in that it has a mandatory screening and testing program. These commitments need to be met.
- Japan is also to be congratulated, in that Japanese scientists are very active in developing screens and tests, including DNA micro-array systems [62]. Moreover, Japan is reportedly to implement a tiered approach to chemical testing consisting of initial sorting, followed (where appropriate) by prescreening, screening, and definitive testing [63].
- Industry groups overseeing research programs tend to "down-play" or miscommunicate the risks. For example, the European Chemical Industry Council (CEFIC) 1999 Newsletter focusing on endocrine disruption concluded the following, "Even though CEFIC's ED research program is yielding results on the potential effects of endocrine disrupters on human health and wildlife, we're still a long way from finding out if or how this is happening" [64]. In contrast to this view, there are many reports showing that endocrine disruption is certainly occurring in wildlife. Indeed, an eminent scientist in the field, Dr. Peter Matthiessen (Centre for Ecology and Hydrology, UK) has said that there is abundant evidence that wildlife is being affected and that endocrine disruption in wildlife is no longer just a hypothesis [65].

- "Public health professionals need to be aware that the 'sound science' movement is not an indigenous effort from within the profession to improve the quality of scientific discourse, but reflects sophisticated public relations campaigns controlled by industry executives and lawyers whose aim is to manipulate the standards of scientific proof to serve the corporate interests of their clients" [66]. Industry should, of course, be entitled to air their views honestly, and such views should be given due consideration, but industry funding should not be hidden.
- The CEFIC has estimated that between 1996 and 2005, it will have allocated about 17 million Euros *in total* to research into endocrine disruption [Taalman, personal communication, 29.01.02]. This is a remarkably small amount, which equates to just 0.004 % of the *annual* value of EU chemicals production.
- There are grounds for criticizing industry's actions to date and for suggesting a certain amount of duplicity. On the one hand, industry wants to be seen to be responsible and tries to show that it has invested a significant amount of money in research, while on the other hand it actually allocates a relatively small proportion of money to research, and seeks to undermine the concerns. That said, it is always difficult to generalize, and some companies are obviously better than others.

### Recommendations

- Government and industry research funding into endocrine disruption should be substantially increased and guaranteed for many years to come, because we are still a long way from understanding the extent of the problem.
- Long-term monitoring of the environment is needed, and this should include both the aquatic and terrestrial environment, and species from all trophic levels.
- More effort is particularly needed to hasten the development of screens and tests for ecotoxicity. Developing OECD test guidelines is always a lengthy process, but there is a need for far more commitment from governments.
- Consideration should be given to reviewing the OECD screening information data sets (SIDS), and enhancing some of the OECD test guidelines with respect to ED effects and/or adding new screens.
- Governments should commit to a comprehensive sorting, screening, and testing program for chemicals to which significant exposure occurs. International coordination is needed to prevent unnecessary duplication of testing.
- In particular, given the concern about endocrine disruption in the EU, the Member States of the EU should agree to a screening and testing strategy for EASs, which should be implemented as far as possible in the forthcoming new EU chemicals legislation.
- More resources and international coordination and effort are needed to speed the development of sophisticated non-animal test methods for screening and testing chemicals for endocrine disruption. However, governments should test chemicals to the extent necessary to protect human health and the environment.
- Substances should be tested at low doses, because there may not be a threshold dose, and the dose–response relationship may not be monotonic.
- In risk assessment, exposure to combinations of substances (cumulative and aggregate risks) must be considered.
- In environmental risk assessment, a more prudent approach (that is, a more cautious approach) should be taken when deciding whether a particular effect might have population-level repercussions. Regulatory frameworks should require "reasonable certainty of no harm".
- Given the increased uncertainty in the risk assessment of EASs, WWF considers that precautionary action to try to eliminate or minimize exposures to EASs is warranted.

## REFERENCES


1. L. Tattersfield, P. Matthiessen, P. Campbell, N. Grandy, R. Lange. SETAC-Europe/OECD/EC Expert Workshop on Endocrine Modulators and Wildlife: Assessment and Testing (EMWAT), SETAC Europe, Brussels (1997).
2. T. Colborn and C. Clement. *Advances in Modern Environmental Toxicology, Vol. XXI, Chemical-Induced Alterations in Sexual and Functional Development: The Wildlife/Human Connection*, Princeton Scientific Publishing, Princeton, NJ (1992).
3. Environment Agency of England and Wales. Endocrine disrupting substances in wildlife: A review of the scientific evidence and strategic response. Environment Agency, Bristol (1998).
4. M. Hewitt and M. Servos. *Water Qual. Res. J. Canada* **36** (2), 191–213 (2001).
5. EU Committee on Toxicity Ecotoxicity and the Environment. *CSTEE Opinion on Human and Wildlife Health Effects of Endocrine-Disrupting Chemicals, with Emphasis on Wildlife and on Ecotoxicology Test Methods*. DGXXIV, Consumer Policy and Consumer Health Protection, Brussels (1999).
6. T. Damstra, S. Barlow, A. Bergman, R. Kavlock, G. Van Der Kraak. Global assessment of the state-of-the-science on endocrine disruptors. International Programme on Chemical Safety (IPCS), WHO (2002).
7. Commission of the European Communities (CEC). White Paper: Strategy for a future Chemicals Policy, 2001 (COM92001) 88 final, CEC, Brussels (2001).
8. P. Matthiessen, Y. Allen, S. Bamber, J. Craft, M. Hurst, T. Hutchinson, S. Feist, I. Katsiadaki, M. Kirby, C. Robinson, S. Scott, J. Thain, K. Thomas. *Mar. Environ. Res.* **54** (3–5), 645–649 (2002).
9. J. Loh. Living Planet Report, WWF International, Gland (2002).
10. B. A. Stein. *Environment* **43** (7), 12–22 (2001).
11. EU Scientific Committee on Toxicity, Ecotoxicity and the Environment (CSTEE). Opinion expressed at the 19$^{th}$ CSTEE plenary meeting, C2/JCD/csteeop/Ter9100/D(0), 9 November, Brussels (2000).
12. Technical Guidance Documents in support of the Commission directive 93/67/EEC on risk assessment for new notified substances and the Commission regulation (EC) 1488/94 on risk assessment for existing substances (2002).
13. D. C. Morse, A. Plug, W. Wesseling, K. J. can den Berg, A. Brouwer. *Toxicol. Appl. Pharmacol.* **139**, 252–261 (1996).
14. J. L. Jacobson and S. W. Jacobson. *N. Engl. J. Med.* **335** (11), 783–78 (1996).
15. S. Patandin, C. I. Lanting, P. G. Mulder, E. R. Boersma, P. J. Sauer, N. Weisglas-Kuperus. *J. Pediatr.* **134** (1), 33–41 (1999).
16. T. Darvill, E. Lonkey, J. Reihman, P. Stewart, P. Pagano. *Neurotoxicology* (6), 1029–1038 (2000).
17. T. J. Kubiak, H. J. Harris, L. M. Smith, T. R. Schwartz, D. L. Stalling, J. A. Trick, L. Sileo, D. E. Docherty, T. C. Erdman. *Arch. Environ. Contam. Toxicol.* **18** (5), 706–727 (1989).
18. G. L. Hunt and M. W. Hunt. *Science* **196**, 1466–1467 (1977).
19. S. A. Fisher, G. R. Bortolotti, K. J. Fernie, J. E. Smits, T. A. Marchant, K. G. Drouillard, D. M. Bird. *Arch. Environ. Contam. Toxicol.* **41** (2), 215–220 (2001).
20. A. E. Quaglino, C. B. Craig-Veit, M. R. Viant, A. L. Erichsen, D. M. Fry, J. R. Millam. *Horm. Behav.* **41** (2), 236–241 (2002).
21. P. Eriksson, E. Jakobsson, A. Fredriksson. *Dioxin 98, Vol. 35, Organohalogen Compounds*, Stockholm (1998).
22. P. Matthiessen, J. McLachlan, P. Myers, I. Callard. *APMIS Supplement* **109** (103), S187–S188 (2001).
23. J. P. Geisy and K. Kannan. *Environ. Sci. Technol.* **35** (7), 1339–1342 (2001).
24. M. P. Longnecker, M. A. Klebanoff, H. Zhou, J. W. Brock. *Lancet* **358** (9276), 110–114 (2001).
25. R. Dietz, M. P. Heide-Jorgensen, T. Harkonen. *Ambio* **18**, 258–264 (1989).

26. H. Van Loveren, P. S. Ross, A. D. Osterhaus, J. G. Vos. *Toxicol. Lett*. **15** (112–113), 319–24 (2000).
27. EU Committee on Toxicity Ecotoxicity and the Environment. *CSTEE Opinion on Human and Wildlife Health Effects of Endocrine Disrupting Chemicals, with Emphasis on Wildlife and on Ecotoxicology Test Methods.* DGXXIV, Consumer Policy and Consumer Health Protection, Brussels (1999).
28. J. E. Fox, M. Starcevic, K. Y. Kow, M. E. Burow, J. A. McLachlan. *Nature* **413**, 128–129 (2001).
29. National Toxicology Program. *Report of the Endocrine Disruptors Low Dose Peer Review,* USA (2001).
30. F. S. vom Saal, B. G. Timms, M. M. Montano, P. Palanza, K. A. Thayer, S. C. Nagel, M. D. Dhar, V. K. Ganjam, S. Parmigiani, W. V. Welshons. *Proc. Natl. Acad. Sci.* **94** (5), 2056–2061 (1997).
31. Institute for Environment and Health and Environment Agency National Centre for Ecotoxicity and Hazardous Substances. The Identification of oestrogenic effects in wild fish – phase II, R & D Technical Report W2-014/TR, principal investigators J. Sumpter, S. Jobling, C. Tyler, Environment Agency, Bristol (2002).
32. E. Silva, N. Rajapakse, A. Kortenkamp. *Environ. Sci. Technol.* **36** (8) (2002).
33. Centers for Disease Control and Prevention. *National Report on Human Exposure to Environmental Chemicals*, Atlanta, USA (2001).
34. P. M. Foster, K. J. Turner, N. J. Barlow. *Toxicologist* **66** (1-S), 233 (2002).
35. K. Gaido, L. You, S. Safe. SCOPE/IUPAC International Symposium on Endocrine Active Substances, program and collective abstracts, November 17–21, Yokohama (2002).
36. P. Sohoni, C. R. Tyler, K. Hurd, J. Caunter, M. Hetheridge, T. Williams, C. Woods, M. Evans, R. Toy, M. Gargas, J. P. Sumpter. *Environ. Sci. Technol.* **35** (14), 17–25 (2001).
37. J. Oehlmann, U. Schulte-Oehlmann, M. Tillmann, B. Markert. *Ecotoxicology* **9**, 383–397 (2000).
38. S. C. Nagel, F. S. vom Saal, K. A. Thayer, M. G. Dhar, M. Boechler, W. V. Welshons. *Environ. Health Perspect*. **105** (1), 70–76 (1997).
39. F. S. Vom Saal, P. S. Cooke, D. L. Buchanan, P. Palanza, K. A. Thayer, S. C. Nagel, S. Parmigiani, W. V. Welshons. *Toxicol. Ind. Health* **14** (1/2), 239–260 (1998).
40. K. L. Howdeshell, A. K. Hotchkiss, K. A. Thayer, J. G. Vandenbergh, F. S. vom Saal. *Nature* **401**, 763–764 (1999).
41. C. Gupta. *Proc. Soc. Exp. Biol. Med.* **224**, 61–68 (2000).
42. M. Sakaue, S. Ohsako, R. Ishimura, S. Kurosawa, J. Yonemoto, C. Tohyama. *J. Occup. Health* **43**, 185–190 (2001).
43. A. S. Al-Hiyasat, H. Darmani, A. M. Elbetieha. *Eur. J. Oral Sci. Apr.* **110** (2), 163–7 (2002).
44. OECD (Organization for Economic Cooperation and Development). *Initiatives to share the burden of the testing and assessment of endocrine disrupting chemicals*, ENV/JM(2001)20, 11 April, OECD, Paris (2001).
45. C. M. Markey, C. L. Michaelson, E. C. Veson, C. Sonnenschein, A. M. Soto. *Environ. Health Perspect*. **109** (1), 55–60 (2001).
46. M. G. Forest, P. C. Sizonenko, A. M. Cathiard, J. Bertrand. *J. Clin. Invest*. **53**, 819–828 (1974).
47. N. J. Bolton, J. Tapanainen, M. Koivisto, R. Vihko. *Clin. Endocrinol*. **31**, 201–207 (1989).
48. B. D. Sachs, R. L. Meisel. In *The Physiology of Reproduction* 1st ed., Vol. 2, E. Knobil and J. Neill (Eds.), pp. 1444–1447, Raven Press, New York (1988).
49. Risk Policy Analysts (RPA). Report from the UK Environment Agency's National Centre for Ecotoxicology and Hazardous Substances Peer Review Group, Consultation on BPA, RPA, Norfolk (2001).
50. H. I. Kwak, M. O. Bae, M. H. Lee, Y. S. Lee, B. J. Lee, K. S. Kang, C. H. Chae, H. J. Sung, J. S. Shin, J. H. Kim, W. C. Mar, Y. Y. Sheen, M. H. Cho. *Environ. Toxicol. Chem.* **20** (4),787–95 (2001).

51. Health Council of the Netherlands. *Hormone Disruptors in Ecosystems.* 1999/13E, Health Council of the Netherlands, The Hague (1999).
52. R. Waldock, H. L. Rees, P. Matthiessen, M. A. Pendle. *J. Mar. Biol. Assoc. UK* **79**, 225–232 (1999).
53. H. L. Rees, R. Waldock, P. Matthiessen, M. A. Pendle. *Mar. Pollut. Bull.* **42**, 137–144 (2001).
54. The Environment Council of the EU, Council conclusions on the Communication from the Commission to the Council and the European Parliament: Community strategy for endocrine disrupters – a range of substances suspected of interfering with the hormone systems of humans and wildlife, 7526/00, Brussels, 7th April 2000. Conclusion 5 stresses "that the precautionary principle must be applied in order to respond quickly and effectively to the problem…". Conclusion 6 considers "that for endocrine disrupters, there is a need to develop quick and effective risk management strategies for substances which may, on the basis of a preliminary scientific evaluation, have potential adverse effects on human health or the environment…".
55. The European Parliament, Resolution A5-0197/2000 on the Commission communication to the Council and the European Parliament on a Community strategy for endocrine disrupters – a range of substances suspected of interfering with the hormone systems of humans and wildlife (COM(1999) 706-C5-0107/2000 – 2000/2071(COS)), October 2000. Paragraph C states "whereas limitations and uncertainties in the available scientific data and, consequently, discrepancies in the observed effects – linked with stated disagreements between scientists as to the importance and/or interpretation of data – must all lead to the application of the precautionary principle".
56. Commission of the European Communities. Communication from the Commission on the precautionary principle, COM(2000)1, Brussels (2000).
57. Environment Council of the European Union. Council Conclusions from their meeting of 7 June on the Commission of the European Communities (CEC). *White Paper: Strategy for a Future Chemicals Policy, 2001 (COM92001) 88 final,* CEC, Brussels (2001).
58. National Academy of Sciences (NAS), National Research Council. *Toxicity Testing, Strategies to Determine Needs and Priorities,* National Academy Press, Washington DC (1984).
59. Environmental Defence Fund (EDF). *Toxic Ignorance*, EDF, Washington DC (1997).
60. US EPA, Office of Pollution Prevention and Toxics. *Chemical Hazard Data Availability Study*, US EPA, Washington DC (1998).
61. R. Allanou, B. G. Hansen, Y. van der Bilt. *Public Availability of Data on EU High Production Volume Chemicals. EUR 18996 EN.* European Commission Joint Research Centre, Italy (1999).
62. OECD. Thought starter paper: Sharing the work on testing and assessment of endocrine disruptors. 15 May 2002. ENV/JM/TG/EDTA(2002)4.
63. OECD. Thought starter paper: Framework for the testing and assessment of endocrine disruptors, 15 May 2002. ENV/JM/TG/EDTA(2002)2.
64. CEFIC. The Long Range Research Initiative Update. Issue 2. The chemical industry's research program on endocrine disruption.
65. The ENDS Report. May, **280**, Environmental Data Services, London (1998).
66. E. K. Ong and S. A. Glantz. *Am. J. Pub. Health* **91** (11), 1749–1757 (2001).